



Dear Doctor:

Thank you for your interest in the enclosed reprint, "Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor, Sitagliptin, Compared With the Sulfonylurea, Glipizide, in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone: A Randomized, Double-Blind, Non-Inferiority Trial," by M.A. Nauck et al, as published in *Diabetes, Obesity and Metabolism*, Volume 9, 2007. The objective of the study was to compare the efficacy and safety of sitagliptin vs glipizide in patients with type 2 diabetes and inadequate glycemic control.

In this study, after 52 weeks, JANUVIA™ (sitagliptin) and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis. These results were consistent with the per protocol analysis. A conclusion in favor of the noninferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (>70% of patients had baseline A1C <8% and >90% had A1C <9%).

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus.

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. JANUVIA has not been studied in combination with insulin.

JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency or with end-stage renal disease requiring hemodialysis or peritoneal dialysis.

As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a class of medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

In clinical studies, the adverse reactions, regardless of investigator assessment of causality, in  $\geq 5\%$  of patients treated with JANUVIA as monotherapy and in combination and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache. In combination with sulfonylurea and with sulfonylurea and metformin, the adverse reaction of hypoglycemia was also reported more commonly with JANUVIA than with placebo.

**Before prescribing JANUVIA, please read the accompanying Prescribing Information.** For additional copies of the Prescribing Information, call 1-800-672-6372, visit [Januvia.com](http://Januvia.com), or contact your Merck representative.

Thank you for your interest in this information about JANUVIA.

Sincerely,

A handwritten signature in black ink, appearing to read "Bram Greenberg".

Bram Greenberg, MD, FAAP  
Executive Director, Medical Services

Enclosure: Prescribing Information for JANUVIA

[Click to view Study Abstract](#)

# **Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial**

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**Aim:** To compare the efficacy and safety of sitagliptin vs. glipizide in patients with type 2 diabetes and inadequate glycaemic control [haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>)  $\geq 6.5$  and  $\leq 10\%$ ] on metformin monotherapy.

**Methods:** After a metformin dose titration/stabilization period ( $\geq 1500$  mg/day), 1172 patients were randomized to the addition of sitagliptin 100 mg q.d. (N = 588) or glipizide 5 mg/day (up-titrated to a potential maximum 20 mg/day) (N = 584) for 52 weeks. The primary analysis assessed whether sitagliptin was non inferior to glipizide regarding HbA<sub>1c</sub> changes from baseline at Week 52 using a per protocol approach.

**Results:** From a mean baseline of 7.5%, HbA<sub>1c</sub> changes from baseline were -0.67% at Week 52 in both groups, confirming non inferiority. The proportions achieving an HbA<sub>1c</sub> < 7% were 63% (sitagliptin) and 59% (glipizide). Fasting plasma glucose changes from baseline were -0.56 mmol/l (-10.0 mg/dl) and -0.42 mmol/l (-7.5 mg/dl) for sitagliptin and glipizide, respectively. The proportion of patients experiencing hypoglycaemia episodes was significantly ( $p < 0.001$ ) higher with glipizide (32%) than with sitagliptin (5%), with 657 events in glipizide treated patients compared with 50 events in sitagliptin treated patients. Sitagliptin led to weight loss (change from baseline -1.5 kg) compared with weight gain (+1.1 kg) with glipizide [between treatment difference (95% confidence interval) -2.5 kg (-3.1, -2.0);  $p < 0.001$ ].

**Conclusions:** In this study, the addition of sitagliptin compared with glipizide provided similar HbA<sub>1c</sub> lowering efficacy over 52 weeks in patients on ongoing metformin therapy. Sitagliptin was generally well tolerated, with a lower risk of hypoglycaemia relative to glipizide and with weight loss compared with weight gain with glipizide.

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